United States Patent [19]

Leinert et al.

[11] 3,976,779

[45] Aug. 24, 1976

[54] 1,2,3,4-TETRAHYDRO-CARBAZOLE COMPOUNDS AND β-ADRENERGIC COMPOSITIONS

[75] Inventors: **Herbert Leinert**, Heppenheim; **Alfred Popelak**, Rimbach; **Kurt Stach**, Mannheim-Waldhof; **Wolfgang Bartsch**, Viernheim; **Karl Dietmann**, Mannheim-Vogelstang, all of Germany

[73] Assignee: **Boehringer Mannheim G.m.b.H.**, Mannheim-Waldhof, Germany

[22] Filed: **Apr. 16, 1975**

[21] Appl. No.: **568,743**

[30] **Foreign Application Priority Data**

May 21, 1974 Germany 2424523

[52] **U.S. Cl.** **424/274**; 260/315

[51] **Int. Cl.²** **A61K 31/40**

[58] **Field of Search** 260/315; 424/274

[56] **References Cited**

UNITED STATES PATENTS

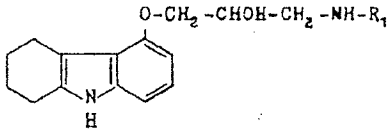
2,731,474	1/1956	Long	260/315
3,663,607	5/1972	Barrett et al.	260/315

Primary Examiner—Sherman D. Winters

Attorney, Agent, or Firm—Burgess, Dinklage & Sprung

[57] **ABSTRACT**

New 1,2,3,4-tetra-hydrocarbazole derivatives of the formula:



(I),

wherein R^1 is straight-chained or branched alkyl, and the pharmacologically compatible salts thereof, are markedly effective as inhibitors of adrogenic β-receptors and thus useful for the treatment and prophylaxis of cardiac and circulatory diseases.

13 Claims, No Drawings

United States Patent [19]

Zölss et al.

[11] Patent Number: 4,767,784

[45] Date of Patent: Aug. 30, 1988

[54] NOVEL CRYSTALLINE SALTS OF ARYLOXY-PROPANOLAMINES, A PROCESS FOR THEIR PREPARATION AND THEIR USE

[76] Inventors: **Gerhard Zölss**, Ziegeleistrasse 72/2, A-4020 Linz; **Gerhard Pfarrhofer**, Schumpeterstrasse 15, A-4040 Linz, both of Austria

[21] Appl. No.: **935,917**

[22] Filed: **Nov. 28, 1986**

[30] **Foreign Application Priority Data**

Dec. 13, 1985 [DE] Fed. Rep. of Germany 3544172

[51] **Int. Cl.**[4] **A61K 31/17**; C07C 127/19; C07C 101/00

[52] **U.S. Cl.** ..... **514/554**; 260/501.11; 260/501.17; 260/501.18; 260/502 R; 514/555; 514/561; 514/563; 514/564; 514/576; 560/19; 560/29; 560/101; 562/471; 562/472; 562/480; 562/490; 562/493; 564/51; 564/52; 564/164; 564/165; 564/169; 564/336; 564/347; 558/303; 558/308

[58] **Field of Search** 564/51, 52, 164, 165, 564/169, 336, 347; 560/101, 19, 29; 260/501.17, 501.11, 501.18, 502; 562/472, 471, 480, 490, 493; 514/554, 555, 561, 563, 564, 576; 558/303, 308

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,079,962	5/1937	Miescher et al.	560/101
3,317,553	5/1967	Crowther et al.	.
3,501,769	3/1970	Crowther et al.	260/501.17
3,723,476	3/1973	Nakanishsi et al.	260/347.7
4,034,009	7/1977	Zolss et al.	564/51
4,038,313	7/1977	Wilhelm	564/51
4,081,447	3/1978	Prasad et al.	260/288 R
4,404,213	10/1983	Haken et al.	424/263
4,460,586	7/1984	Berthold	544/373

FOREIGN PATENT DOCUMENTS

1061341	8/1979	Canada	564/51
1061342	8/1979	Canada	564/51
3309595	9/1984	Fed. Rep. of Germany	564/51
1383899	2/1975	United Kingdom	564/51
1396322	6/1975	United Kingdom	564/51

OTHER PUBLICATIONS

Crowther et al.; Beta-Andrenergic Blocking Agents; M. Med. Chem. (1971), vol. 14, 511-513.

Nakanishi et al.; Studies on Cardiovascular Drugs; J. Med. Chem. (1972), vol. 15, 45-48.

Bartsch et al.; Arzneim-Forsch, 27(1) Nr. 5 (1977), 1022-1026.

Chemical Abstracts; vol. 102 (1985) Nr. 72332g.

Primary Examiner—Glennon H. Hollrah

Assistant Examiner—Raymond Covington

[57] **ABSTRACT**

The invention relates to novel crystalline salts of aryloxypropanolamines with diphenylacetic acid, a process for their preparation and the use of these salts for the preparation of chemically pure aryloxy-propanolamines or pharmaceutically acceptable salts thereof.

4 Claims, No Drawings

United States Patent [19]

Zöl et al.

[11] Patent Number: 4,849,530

[45] Date of Patent: Jul. 18, 1989

[54] PROCESS FOR THE PREPARATION OF CRYSTALLINE SALTS OR ARYLOXY-PROPANOLAMINES

[75] Inventors: Gerhard Zöl; Gerhard Pfarrhofer, both of Linz, Austria

[73] Assignee: Rorer Pharmaceutical Corporation, Fort Washington, Pa.

[21] Appl. No.: 203,390

[22] Filed: Jun. 6, 1988

Related U.S. Application Data

[62] Division of Ser. No. 935,917, Nov. 28, 1986, Pat. No. 4,767,784.

[30] Foreign Application Priority Data

Dec. 13, 1985 [DE] Fed. Rep. of Germany 3544172

[51] Int. Cl.[4] C07C 127/19; C07C 101/00

[52] U.S. Cl. 549/491; 558/303; 558/308; 560/19; 560/20; 560/101; 562/471; 562/472; 562/486; 562/490; 562/492; 562/491; 564/51; 564/52; 564/164; 564/165; 564/336; 564/347

[58] Field of Search 564/51, 52, 164, 165, 564/169, 336, 347; 260/501.17, 501.11, 501.18, 502; 558/303, 308; 549/491; 560/19, 20, 101; 562/471, 472, 486, 490, 493

[56] References Cited

U.S. PATENT DOCUMENTS

2,079,962	5/1937	Miescher et al.	560/101
3,317,553	5/1967	Crowther et al.	260/501.17
3,501,769	3/1970	Crowther et al.	260/501.17
3,723,476	3/1973	Nakanishi et al.	260/501.17
4,034,009	7/1977	Zolss et al.	564/54
4,038,313	7/1977	Wilhelm	564/51
4,081,447	3/1978	Prasad et al.	562/427
4,460,586	7/1984	Berthold	544/313
4,767,784	8/1988	Zölss et al.	514/554

FOREIGN PATENT DOCUMENTS

1061341	8/1979	Canada	564/51
1061342	8/1979	Canada	564/51
3309595	9/1984	Fed. Rep. of Germany	564/51
1383899	2/1975	United Kingdom	564/51
1396322	6/1975	United Kingdom	564/51

OTHER PUBLICATIONS

Crowther et al.; Beta-Andrenergic Blocking Agents; M.Med.Chem (1971), vol. 14, 511-513.

Nakanishi et al.; Studies on Cardiovascular Drugs; J. Med. Chem (19/2), vol. 15, 45-48.

Bartsch et al.; Arzneim-Forsch, 27(1) Nr. 5 (1977), 1022-1026 Chemical Abstracts; vol. 102 (1985), No. 72332 g.

Primary Examiner—Richard L. Raymond
Assistant Examiner—Raymond Covington

[57] ABSTRACT

The invention relates to novel crystalline salts of aryloxypropanolamines with diphenylacetic acid, a process for their preparation and the use of these salts for the preparation of chemically pure aryloxy-propanolamines or pharmaceutically acceptable salts thereof.

4 Claims, No Drawings

United States Patent [19]

Mai et al.

[11] Patent Number: 4,990,668

[45] Date of Patent: Feb. 5, 1991

[54] OPTICALLY ACTIVE ARYLOXYPROPANOLAMINES AND ARYLETHANOLAMINES

[75] Inventors: **Khuong H. X. Mai**, Waukegan; **Ghanshyam Patil**, Vernon Hills; **William L. Matier**, Libertyville, all of Ill.

[73] Assignee: **E. I. Du Pont de Nemours and Company**, Wilmington, Del.

[21] Appl. No.: **804,407**

[22] Filed: **Dec. 4, 1985**

[51] **Int. Cl.**[5] C07C 215/08; C07C 217/54

[52] **U.S. Cl.** **564/349**; 544/134; 544/169; 544/224; 544/312; 546/159; 548/135; 548/186; 548/247; 548/305; 548/444; 548/503; 548/509; 548/515; 549/23; 549/289; 549/304; 549/387; 549/466; 549/468; 549/487; 549/491; 558/401; 558/422; 560/29; 560/38; 560/42; 564/51; 564/79; 564/86; 564/165; 564/220; 564/363

[58] **Field of Search** 544/134, 169, 224, 312; 546/158; 548/135, 186, 247, 305, 444, 503, 504, 515; 549/23, 289, 304, 387, 466, 468, 487, 491; 558/401, 422; 560/29, 35, 42; 564/51, 86, 165, 220, 79, 363, 349

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,850,946	11/1974	Edwards	564/374 X
4,202,978	5/1980	Fohrenholtz et al.	564/349 X
4,582,905	4/1986	Sakai	564/349 X

FOREIGN PATENT DOCUMENTS

56-123854	9/1981	Japan	564/349

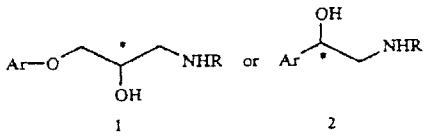
OTHER PUBLICATIONS

Iriuchijima et al., "Agric. Biol. Chem.", vol. 46, No. 5, pp. 1153–1157 (1982).

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Gildo E. Fato

[57] **ABSTRACT**

Described is a process for preparing a racemic or chiral aryloxypropanolamine (1) or arylethanolamine (2) of the formula



1 2

wherein Ar is aryl, substituted aryl, heteroaryl, or aralkyl and R is alkyl, substituted alkyl, aralkyl, or WB wherein W is a straight or branched chain alkylene of from 1 to about 6 carbon atoms and wherein B is $—NR_2COR_3$, $—NR_2CONR_3R_4$, $—NR_2SO_2R_3$, $—NR_2SO_2NR_3R_4$, or $—NR_2COOR_5$, where R_2, R_3, R_4, and R_5 may be the same or different and may be hydrogen, alkyl, alkoxyalkyl, alkoxyaryl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or aralkyl, except that R_3 and R_5 are not hydrogen when B is $—NR_2SO_2R_3$ or $—NR_3COOR_5$, or R_3 and R_4 may together with N form a 5- to 7-membered heterocyclic group.

The process can be used to prepare beta-blocking agents, useful in the treatment of cardiac conditions.

7 Claims, No Drawings

United States Patent [19]

Leinert

[11] Patent Number: 5,071,868

[45] Date of Patent: Dec. 10, 1991

[54] PROCESS FOR THE PREPARATION OF OPTICALLY-ACTIVE CARBAZOLE DERIVATIVES, NEW R- AND S-CARBAZOLE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS

[75] Inventor: Herbert Leinert, Heppenheim, Fed. Rep. of Germany

[73] Assignee: Boehringer Mannheim GmbH, Mannheim, Fed. Rep. of Germany

[21] Appl. No.: 631,641

[22] Filed: Jan. 28, 1991

Related U.S. Application Data

[62] Division of Ser. No. 299,750, Jan. 19, 1989, Pat. No. 4,985,454.

[30] **Foreign Application Priority Data**

May 26, 1983 [DE] Fed. Rep. of Germany 3319027

[51] Int. Cl.[5] **A61K 31/40**; C07D 209/82; C07D 401/12; C07D 491/056

[52] U.S. Cl. **514/411**; 514/302; 514/339; 514/913; 514/929; 546/115; 546/116; 546/272; 548/444

[58] **Field of Search** 548/444; 546/115, 116, 546/272; 514/302, 339, 411, 929, 913

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,503,067	3/1985	Wiedemann et al.	514/411
4,760,085	7/1988	Bartsch	514/411

FOREIGN PATENT DOCUMENTS

2815926 10/1979 Fed. Rep. of Germany .

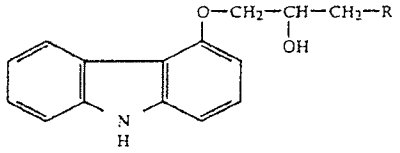
Primary Examiner—Richard L. Raymond

Assistant Examiner—P. O'Sullivan

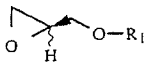
Attorney, Agent, or Firm—Felfe & Lynch

[57] ABSTRACT

A process for the preparation of S- or R-carbazole derivatives of the general formula:



in which R is an unsubstituted or substituted amino radical and pharmacologically acceptable salts, by either reacting R-(−)-epichlorohydrin (for the S-carbozole derivative); or reacting an S-epoxide derivative of the general formula:



in which R_1 is the residue of a substituted sulphonic acid derivative (for the R-carbazole derivative); with 4-hydroxycarbazole and then with ammonia or a substituted amine of the general formula RH, and recovering the compound or converting it to a pharmacologically acceptable salt.

The new R-(+)- and S(−)-carbazole derivatives provided by the inventive process have unexpected beta blocking and vasodilatory properties and are useful in pharmaceutical compositions. R-(+)-carbazole derivatives are also useful for the treatment of glaucoma.

6 Claims, No Drawings

US006140352A

United States Patent [19]

Crowell et al.

[11] Patent Number: 6,140,352

[45] Date of Patent: *Oct. 31, 2000

[54] CARBAZOLYL-SUBSTITUTED ETHANOLAMINES AS SELECTIVE β_3 AGONISTS

[75] Inventors: Thomas A. Crowell; Deborah A. Evrard; Charles D. Jones; Brian S. Muehl, all of Indianapolis; Christopher J. Rito, Mooresville; Anthony J. Shuker, Indianapolis, all of Ind.; Andrew J. Thorpe, Ann Arbor, Mich.; Kenneth J. Thrasher, Indianapolis, Ind.

[73] Assignee: Eli Lilly and Company, Indianapolis, Ind.

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: 09/068,192

[22] PCT Filed: Aug. 28, 1997

[86] PCT No.: PCT/US97/15230

§ 371 Date: May 4, 1998

§ 102(e) Date: May 4, 1998

[87] PCT Pub. No.: WO98/09625

PCT Pub. Date: Mar. 12, 1998

Related U.S. Application Data

[60] Provisional application No. 60/025,818, Sep. 5, 1996, and provisional application No. 60/029,228, Oct. 30, 1996.

[51] Int. Cl.[7] A61K 31/4439; C07D 401/12

[52] U.S. Cl. 514/339; 514/323; 514/411; 514/374; 514/397; 514/381; 546/200; 546/276.7; 548/238; 548/252; 548/311.4; 548/444

[58] Field of Search 546/276.7, 200; 548/444, 238, 252, 311.4; 514/323, 339, 411, 374, 397, 381

[56] References Cited

U.S. PATENT DOCUMENTS

4,032,575	6/1977	Ikezaki et al.	260/570.6
4,140,789	2/1979	Jaeggi et al. .	
4,235,919	11/1980	Berthold .	
4,288,452	9/1981	Sombroek et al.	424/304
4,309,443	1/1982	Smith et al.	424/319
4,310,527	1/1982	Jaeggi et al. .	
4,338,333	7/1982	Ainsworth et al.	424/309
4,346,093	8/1982	Friebe et al.	424/269
4,367,235	1/1983	Ross et al.	424/273 B
4,385,066	5/1983	Ainsworth et al.	424/309
4,391,826	7/1983	Mills et al.	424/324
4,396,627	8/1983	Ainsworth et al.	424/309
4,432,993	2/1984	Ferris	424/285
4,478,849	10/1984	Ainsworth et al.	424/285
4,497,813	2/1985	Ostermayer et al.	514/166
4,503,067	3/1985	Wiedemann et al.	514/411
4,513,001	4/1985	Joannic et al.	514/394
4,636,511	1/1987	Ostermayer et al.	514/311
4,652,679	3/1987	Alig et al.	564/86
4,697,022	9/1987	Leinert	548/444
4,727,067	2/1988	Ostermayer et al.	514/162
4,751,246	6/1988	Philion	514/649
4,772,631	9/1988	Holloway et al.	514/539
4,892,886	1/1990	Alig et al.	514/567
4,940,800	7/1990	Bertolini et al.	548/327
4,960,783	10/1990	Bonse et al.	514/387
4,977,148	12/1990	Holloway et al.	514/183
5,013,761	5/1991	Beedle et al.	514/650
5,064,863	11/1991	Alig et al.	514/563
5,166,218	11/1992	Alig et al.	514/652
5,254,595	10/1993	Guzzi et al.	514/652
5,321,036	6/1994	Sher	514/365
5,393,772	2/1995	Yue et al.	514/410
5,420,294	5/1995	Beedle et al.	548/507
5,453,436	9/1995	Ohlstein	514/411
5,488,151	1/1996	Baroni et al.	562/452
5,534,640	7/1996	Tegeler et al.	549/80
5,541,197	7/1996	Fisher et al.	514/311
5,541,204	7/1996	Sher et al.	514/359
5,561,142	10/1996	Fisher et al.	514/312
5,574,164	11/1996	Tegeler et al. .	
5,776,983	7/1998	Washburn et al. .	

FOREIGN PATENT DOCUMENTS

0 040 000	11/1981	European Pat. Off.	C07C 91/02
0 052 963	6/1982	European Pat. Off.	C07C 93/14
0 061 907	10/1982	European Pat. Off.	C07C 91/16
0 063 004	10/1982	European Pat. Off.	C07C 101/28
0 066 351	12/1982	European Pat. Off.	C07C 93/14
0 068 669	1/1983	European Pat. Off.	C07C 91/16
0 070 134	1/1983	European Pat. Off.	C07C 93/14
0 082 665	6/1983	European Pat. Off.	C07D 333/38

(List continued on next page.)

OTHER PUBLICATIONS

Neugebauer et al., CA 117:39731, 1992.

G. Neugebauer and P. Neubert "Metabolism of carvedilol in man" *European Journal of Drug Metaboolism and Pharmacokinetics* 16 (4) :257–260 (1991).

S. L. Heald, et al. "Synthesis of Iodine–125 labeled 14–(4–Azidobenzyl)Carazolol: A Potent Beta Adrenergic Photoaffinity Probe" *J. Med. Chem.* 26: (6) :832–838 (1983).

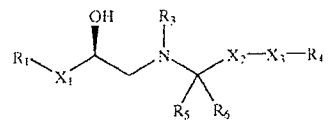
(List continued on next page.)

Primary Examiner—Laura L. Stockton

Attorney, Agent, or Firm—Gilbert T. Voy

[57] ABSTRACT

Disclosed herein are selective beta 3 adrenergic agonists represented by the following structural formula:



The variables in the structural formula shown above are defined in the specification. Also disclosed are methods of using these compounds for agonizing the beta 3 adrenergic receptor in patients in need of such treatment, for example, patients in need of treatment for obesity or Type II diabetes.

41 Claims, No Drawings

US006939986B2

(12) **United States Patent**
Karpf et al.

(10) Patent No.: US 6,939,986 B2
(45) Date of Patent: Sep. 6, 2005

(54) PROCESS FOR PREPARING 1,2-DIAMINO COMPOUNDS

(75) Inventors: **Martin Karpf**, Reinach (CH); **René Trussardi**, Birsfelden (CH)

(73) Assignee: **Hoffmann-La Roche Inc.**, Nutley, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/081,345**

(22) Filed: **Feb. 22, 2002**

(65) **Prior Publication Data**

US 2002/0095040 A1 Jul. 18, 2002

Related U.S. Application Data

(62) Division of application No. 09/590,317, filed on Jun. 8, 2000.

(30) **Foreign Application Priority Data**

Jun. 11, 1999 (EP) 99111418
Feb. 21, 2000 (EP) 00103588

(51) **Int. Cl.**[7] **C07C 227/08**; C07C 247/14; C07D 317/44

(52) **U.S. Cl.** **560/29**; 560/125; 560/128; 560/169; 546/146; 549/436; 549/546; 549/961; 514/237.5; 514/351; 514/454; 564/135; 548/477

(58) **Field of Search** 560/125, 128, 560/169, 29; 549/436, 546, 961; 546/146; 514/237.5, 351, 454; 564/135; 548/477

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,763,483	A	*	6/1998	Bischofberger et al.	
5,859,284	A	*	1/1999	Kent et al.	
5,866,601	A	*	2/1999	Lew et al.	
5,886,213	A	*	3/1999	Kent et al.	
5,952,375	A	*	9/1999	Bischofberger et al.	
5,994,377	A	*	11/1999	Kim et al.	
6,057,459	A	*	5/2000	Kent et al.	
6,204,398	B1	*	3/2001	Kent et al.	549/436
6,437,171	B1	*	8/2002	Karpf et al.	560/125
6,518,438	B2	*	2/2003	Kent et al.	548/961
2002/0058823	A1	*	5/2002	Kent et al.	549/436
2002/0156300	A1	*	10/2002	Kent et al.	549/436

FOREIGN PATENT DOCUMENTS

FR	1559511	*	3/1969
WO	WO 96/26933	*	9/1996
WO	WO 98/07685	*	2/1998
WO	WO 99/14185	*	3/1999

OTHER PUBLICATIONS

Auge et al. Tetrahedron Letters, 37(43), pp 7715–7716, 1996.*

K.G. Akamanchi, et. al., "Diisopropoxyaluminium Trifluroacetate: A New off the Shelf Metal Alkoxide Type Reducing Agent for Reduction of Aldehydes and Ketones," Synlett, 371–372 (1997).

C. Anaya de Parrodi, et. al. "Application of Phosphorylated Reagents Derived from N,N[1]–di–[(S)–α–phenylethyl]cyclohexane–1,2–diamines in the Determination of the Enantiomeric Purity of Chiral Alcohols," Tetrahedron: Asymmetry, 9, 2093–2099 (1998).

C. Anaya de Parrodi, et. al., "Synthesis of Enantiomerically Pure N–(S)–α–Methylbenzylβ–Aminoalcohols by Regio– and Stereoselective Ring Opening of Epoxides," An Quim. Int. Ed., 92, 400–404 (1996).

A.P.A. Arbore, et. al., "A Rapid Approach to Amino–Acid Derivatives by [2,3]–Stevens Rearrangements" Synlett, 2, 236–38 (2000).

J. Auge, et. al., "Lithium Trifluoromethanesulfonate–catalysed Aminolysis of Oxiranes," Tetrahedron Lett. 37, 7715–7716 (1996).

P. Barbaro, et. al., "New Enantiomerically Pure Aminoalcohols from (R)–α–Methylbenzylamine and Cyclohexene Oxide," Tetrahedron: Asymmetry 7, 843–850 (1996).

M. Beaton, et. al., "Synthesis of 6–Amino–3,5–deoxyinositol 1–Phosphates via (1R,2R,4R,6S)–1,6 Epoxy–2,4–bis–benzyloxycyclohexane Aminolysis in Aqueous Ytterbium Triflate Solution," Tetrahedron Lett., 39, 8549–8552 (1998).

F. Brion "On the Lewis Acid Catalyzed Diels–Alder reaction of Furan. Regio–and Stereospecific Synthesis of Substituted Cyclohexenols and Cyclohexadienols," Tetrahedron Letters, 23, 5299–5302 (1982).

F.M. Callahan, et. al., "The Tertiary Buyl Group as a Blocking Agent for Hydroxyl Sulfhydryl and Amino Functions in Peptide Synthesis" J. Am. Chem. Soc. 85, 201–7 (1963).

M. Canas, et. al., "Regioselective Ring Opening of Chiral Epoxyalcohols by Primary Amines," Tetrahedron Lett. 32, 6931–6934 (1991).

M. Chini, et. al. "Metal Salts as New Catalysts for Mild and Efficient Aminolsis of Oxiranes," Tetrahedron Lett. 31, 4661–4664 (1990).

M. Chini, et. al. "Regioalternating Selectivity in the Metal Salt Catalyzed Aminolysis of Styrene Oxide," J. Org. Chem. 56, 5939–5942 (1991).

(Continued)

Primary Examiner—James O. Wilson
Assistant Examiner—Devesh Khare
(74) *Attorney, Agent, or Firm*—George W. Johnston; Dennis P. Tramaloni; Samuel H. Megerditchian

(57) **ABSTRACT**

The invention provides a multistep process for preparing 1,2-diamino compounds and pharmaceutically acceptable addition salts thereof from 1,2-epoxides.

2 Claims, No Drawings

17卷5期 结 构 化 学 (JIEGOU HUAXUE) Vol. 17, No. 5
1998. 9. Chinese J. Struct. Chem. Sept. 1998

Synthesis and Crystal Structure of Carvedilol

CHEN Wei-Min[1] ZENG Long-Mei[2] YU Kai-Bei[3] XU Ji-Hong[1]
([1] *Institute of Pharmaceutical Sciences, the First Military Medical University, Guangzhou, 510515;* [2] *Department of Chemistry, Zhongshan University, Guangzhou 510275;* [3] *Chengdu Institue of Analysis and Measurement, the Chinese Academy of Sciences, Chengdu 610041*)

ABSTRACT The crystal structure of the title compound carvedilol, $C_{24}H_{26}N_2O_4$ (M_r = 406.47), has determined by single-crystal X-ray diffraction. The crystal is monoclinic with space group $P2_1/c$, a=9.094(1), b=12.754(1), c=18.330(2) Å, β=97.36(1)°, V=2108.5(4) Å^3, Z=4, D_c=1.280 g/cm^3, $F(000)$=864, μ=0.088 mm^{-1} and final R=0.0368, $wR(F^2)$=0.0787 for reflections ($I>2\sigma(I)$). X-ray analysis reveals that the crystal is composed of a pair of enantiomer, and there are hydrogen bonds O(3)—H(30)—N(1) between the two enantimers. There are two planes in the molecule.

Keywords: carvedilol, synthesis, crystal structure

1 INTRODUCTION

Carvedilol, 1-(4-carbazolyloxy)-3-[2-methoxyphenoxy) ethylamino]-2-propanol, is a new β-blocking and vasodilating agent[1]. It had synthesized by F. Wiedemann *et al*[2]. However the report about crystal structure of carvedilol has not been seen. In this paper, we discuss the crystal structure of the carvedilol synthesized[2] by the reaction of 4-(2,3-exoxypropoxy)-carbazole and 2-(2-methoxyphenoxy) ethylamine. Since knowledge of the molecular and crystal structure of carvedilol was considered useful for understanding the mechanism of the action on the receptor, the X-ray crystallographic study was carried out.

2 EXPERIMENTAL

2.1 Synthesis[2] 4-(2,3-Epoxypropoxy)-carbazole (10g, 42mmol) and 2-(2-methoxyphonoxy)-ethylamine (10g, 60 mmol) in 50 ml glycol dimethyl ether were stirred for 25 h at 50 ℃. The reaction mixture was evaporated to dryness in a Rotavapor and the residue was stirred in 115ml toluol, 35 ml cyclohexane and 40 ml ethyl acetate, and recrystallized from ethyl acetate with the use of activecharcoal. 10.4 g(61%) of the title compound were afforded. The single crystals suitable for X-ray analysis were obtained from the mixture solvent of toluol, cyclohexane and

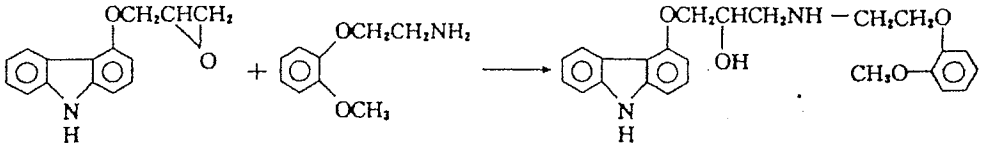
Received 2 January 1998; accepted 26 May 1998

ethyl acetate. mp: 114～115 ℃; Calcd. for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found C, 70.75; H, 6.60; N, 6.72. IR(KBr): ν (N—H, O—H)3346(s), (aryl-H)3087(w), 1609(s), 1588(s), 1503(s), 1447(s) cm^{-1}. NMR: δ_H 1.8 (s, 2H, O—H, $N_{(1)}$—H), 3.1 (m, 4H, $C_{(9)}H_2NC_{(10)}H_2$), 3.8 (s, 3H, OCH_3), 4.2 (m, 5H, $C_{(12)}H_2C_{(11)}H$, $C_{(8)}H_2$), 6.7 (d, 1H, $C_{(15)}H$), 6.9 (s, 4H, $C_{(3-6)}H_4$), 7.1 (d, 1H, $C_{(16)}H$), 7.4～7.2 (m, 4H, $C_{(22-24)}H_3$), 8.20 (d, 1H, $N_{(2)}H$), 8.30(d, 1H, $C_{(14)}H$). MS: m/z 406.2(M^+, 17.7%).

2.2 Structure determination A single crystal with dimensions of 0.66mm × 0.52mm × 0.52mm was selected for X-ray diffraction analysis. All intensity data were collected on a Siemens P_4 diffractometer with graphite monochromated Mo$K\alpha$(λ = 0.71073 Å) radiation using ω scan mode. A total of 4081 reflections were collected in the range of $1.95<\theta<24.96°$ at the temperature of 295 K, of which 2096 independent observed reflections with $I>2\sigma(I)$ were used in the structure determination and refinement. The structure was solved by direct methods and succeeding difference Fourier synthesis. A full-matrix least-squares refinement gave final R = 0.0368 and wR = 0.0787 with $W=1/[\sigma^2(F_o)^2+(0.0501P)^2]$ and $P=[\max(F_o^2, 0)+2F_o^2]/3$, $(\Delta/\sigma)_{max}$ = 0.004, S = 0.860. The program for structure solution and refinement is SHELXTL 5.03.

3 RESULTS AND DISCUSSION

The title compound was prepared from 4-(2,3-epoxypropoxy)-carbazole and 2-(2-methoxyphonoxy) ethylamine as following equation:



The ORTEP plot of the carvedilol with the H atoms is shown in Fig. 1. The unit cell packing of the carvedilol is shown in Fig. 2. Atomic coordinates and thermal parameters are listed in Table 1. The selected bond lengths and angles are given in Table 2 and Table 3, respectively.

Fig. 2 shows that the crystal is composed of a pair of enantiomers, C(11) is a chiral carbon. The angle of O(3)—C(11)—C(10) is 110.5(2)°, that of C(12)—C(11)—C(10) is 110.4(2)°, which are larger than normal 109.5(2)°, the angle of O(3)—C(11)—C(12) is 107.13°, which is slightly less than normal 109.5°. The atoms C(1), O(1), C(2), C(3), C(4), C(5), C(6), C(7) are on one plane, plane equation: $-2.846X+12.021Y-1.391Z+4.9410=0$. While the atoms C(13), C(14), C(15), C(16), C(17), C(18), N(2), C(19), C(20), C(21),

C(22), C(23), C(24) are on the another plane. plane equation $-2.470X+11.564Y-5.228Z+2.1566=0$.

Table 1. Atomic Coordinates and Thermal Parameters(Å²)

Atom	*x*	*y*	*z*	*Ueq*	Atom	*x*	*y*	*z*	*Ueq*
O(1)	0.6502(1)	−0.2750(1)	−0.1120(1)	0.069	C(10)	0.5423(2)	−0.0937(2)	0.1254(1)	0.061
O(2)	0.8405(1)	−0.2127(1)	−0.0057(1)	0.067	C(11)	0.4035(2)	−0.0314(2)	0.0987(1)	0.056
O(3)	0.3346(2)	−0.0714(1)	0.0299(1)	0.075	C(12)	0.2915(2)	−0.0409(2)	0.1528(1)	0.050
O(4)	0.3617(1)	−0.0015(1)	0.2218(1)	0.061	C(13)	0.2817(2)	0.0031(1)	0.2803(1)	0.055
N(1)	0.6482(2)	−0.0943(1)	0.0719(1)	0.058	C(14)	0.1396(2)	−0.0352(2)	0.2810(1)	0.070
N(2)	0.3756(2)	0.1060(1)	0.4609(1)	0.068	C(15)	0.0697(2)	−0.0232(2)	0.3439(1)	0.080
C(1)	0.5335(3)	−0.2973(3)	−0.1699(2)	0.096	C(16)	0.1358(2)	0.0251(2)	0.4059(1)	0.078
C(2)	0.7837(2)	−0.2442(1)	−0.1312(1)	0.054	C(17)	0.2802(2)	0.0608(1)	0.4056(1)	0.058
C(3)	0.8180(3)	−0.2439(2)	−0.2018(1)	0.073	C(18)	0.3543(2)	0.0498(1)	0.3436(1)	0.049
C(4)	0.9535(3)	−0.2108(2)	−0.2156(1)	0.088	C(19)	0.5017(2)	0.0899(1)	0.3632(1)	0.049
C(5)	1.0573(3)	−0.1773(2)	−0.1605(2)	0.084	C(20)	0.5114(2)	0.1234(1)	0.4368(1)	0.056
C(6)	1.0243(2)	−0.1758(2)	−0.0875(1)	0.070	C(21)	0.6419(3)	0.1617(2)	0.4745(1)	0.072
C(7)	0.8873(2)	−0.2091(1)	−0.0737(1)	0.052	C(22)	0.7628(3)	0.1668(2)	0.4378(1)	0.079
C(8)	0.8994(2)	−0.1381(2)	0.0482(1)	0.065	C(23)	0.7563(2)	0.1371(2)	0.3648(1)	0.072
C(9)	0.7931(2)	−0.1338(2)	0.1041(1)	0.064	C(24)	0.6274(2)	0.0986(2)	0.3270(1)	0.059

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 2. Selected Bond Lengths (Å)

Bond	Dist.	Bond	Dist.	Bond	Dist.	Bond	Dist.
O(1)−C(1)	1.429(3)	N(2)−C(17)	1.374(2)	C(8)−C(9)	1.497(3)	C(17)−C(18)	1.400(2)
O(1)−C(2)	1.365(2)	N(2)−C(20)	1.382(2)	C(10)−C(11)	1.518(2)	C(18)−C(19)	1.437(2)
O(2)−C(7)	1.368(2)	C(2)−C(3)	1.370(2)	C(11)−C(12)	1.514(2)	C(19)−C(20)	1.407(2)
O(2)−C(8)	1.424(2)	C(2)−C(7)	1.394(2)	C(13)−C(14)	1.383(2)	C(19)−C(24)	1.398(2)
O(3)−C(11)	1.430(2)	C(3)−C(4)	1.357(3)	C(13)−C(18)	1.394(2)	C(20)−C(21)	1.384(2)
O(4)−C(12)	1.431(2)	C(4)−C(5)	1.360(3)	C(14)−C(15)	1.395(3)	C(21)−C(22)	1.362(3)
O(4)−C(13)	1.372(2)	C(5)−C(6)	1.408(3)	C(15)−C(16)	1.363(3)	C(22)−C(23)	1.385(3)
N(1)−C(9)	1.462(2)	C(6)−C(7)	1.371(2)	C(16)−C(17)	1.391(3)	C(23)−C(24)	1.374(2)
N(1)−C(10)	1.459(2)						

Table 3. Selected Bond Angles (°)

Angle	(°)	Angle	(°)	Angle	(°)
C(1)−O(1)−C(2)	117.9(2)	O(2)−C(8)−C(9)	106.3(2)	C(16)−C(17)−C(18)	121.6(2)
C(7)−O(2)−C(8)	118.40(14)	N(1)−C(9)−C(8)	111.4(2)	C(13)−C(18)−C(17)	119.5(2)
C(12)−O(4)−C(13)	118.95(14)	N(1)−C(10)−C(11)	112.4(2)	C(13)−C(18)−C(19)	133.4(2)
C(9)−N(1)−C(10)	111.74(14)	O(3)−C(11)−C(10)	110.5(2)	C(17)−C(18)−C(19)	107.0(2)
C(17)−N(2)−C(20)	109.7(2)	O(3)−C(11)−C(12)	107.13(14)	C(18)−C(19)−C(20)	106.83(14)
O(1)−C(2)−C(3)	124.1(2)	C(10)−C(11)−C(12)	110.4(2)	C(18)−C(19)−C(24)	134.7(2)
O(1)−C(2)−C(7)	115.83(14)	O(4)−C(12)−C(11)	106.8(2)	C(20)−C(19)−C(24)	118.5(2)
C(3)−C(2)−C(7)	120.0(2)	O(4)−C(13)−C(14)	125.6(2)	N(2)−C(20)−C(19)	108.0(2)
C(2)−C(3)−C(4)	119.9(2)	O(4)−C(13)−C(18)	115.32(14)	N(2)−C(20)−C(21)	129.9(2)
C(3)−C(4)−C(5)	121.3(2)	C(14)−C(13)−C(18)	119.1(2)	C(19)−C(20)−C(21)	122.1(2)
C(4)−C(5)−C(6)	119.9(2)	C(13)−C(14)−C(15)	119.6(2)	C(20)−C(21)−C(22)	117.7(2)
C(5)−C(6)−C(7)	118.7(2)	C(14)−C(15)−C(16)	122.7(2)	C(21)−C(22)−C(23)	121.8(2)
O(2)−C(7)−C(2)	114.8(1)	C(15)−C(16)−C(17)	117.4(2)	C(22)−C(23)−C(24)	120.9(2)
O(2)−C(7)−C(6)	125.1(2)	N(2)−C(17)−C(16)	129.9(2)	C(19)−C(24)−C(23)	119.0(2)
C(2)−C(7)−C(6)	120.1(2)	N(2)−C(17)−C(18)	108.5(2)		

The X-ray crystallographic analysis shows that there is a hydrogen bond O(3)−H(30)−N(1) between the two enantiomers, the distance of O(3)−N(1) is 2.837

Å, and the bond length O(3)—H(3) is 1.139 Å, hydrogen bond length of H(30)—N(1) is 1.730 Å. The angle of O(3)—H(30)—N(1) is 173.1°.

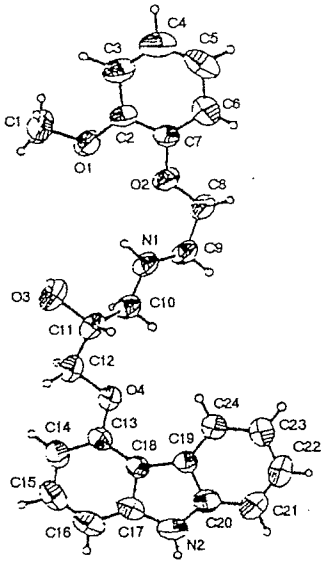


Fig. 1 Structure of carvedilol

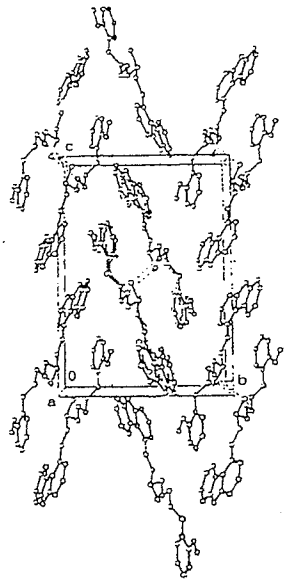


Fig. 2 Packing of the molecules in a unit cell

In vitro in vestigations with the purified stereoisomers of carvedilol show that β_1-adrenoceptor blockade can be attributed primarily to the S(—)-enantiomer. In contrast, both enantiomers exhibit similar α_1-adrenergic blocking activity[3]. Thus, the configuration of chiral carbon C(11) is related to the structure of β_1-adrenoceptor, and not related to the structure of α_1-adrenoceptor. The following illustration was thought[4] as structure-activity relationship of carvedilol. The data of this paper will be useful for understanding the activity center of α_1-adrenoceptor and β_1-adrenoceptor.

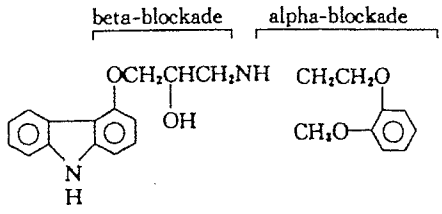


Fig. 3 Structure-activity relationship of carvedilol

REFERENCES

1 Zhou Bing, Wei Er-Qing. β-adrenoceptor antagonist carvedilol(β-受体阻滞药卡维地洛). *Zhongguo Xinyao Zazhi*, 1996, 5(1):23~26

2 Wiedemann F, Kampe W, Thiel M. Carbazolyl-(4)-oxypropanolamine compounds and therapeutic compositions. US patent, 4503067, 1985~03~05

3 Metaviah D, Campoli-Richards D, Sorkin E M. Carvedilol. *Drugs*, 1993, 45(2): 232~258

4 Yue T L, Mckenna P J, Gu J L *et al*. Carvedilol, a new vasodilating adrenoceptor blocker antihypertensive drug, protects endothelial cells from damage initiated by xanthine-xanthine oxidase and neutrophils. *Cardiovascular Research*, 1994, 28: 400~406